UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/807,509	06/25/2001	Fritz Grunert	24741-1523	9439

26633 7590 04/22/2003

HELLER EHRMAN WHITE & MCAULIFFE LLP
1666 K STREET,NW
SUITE 300
WASHINGTON, DC 20006

EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	PAPER NUMBER
1632	12

DATE MAILED: 04/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/807,509	Grunert
Examiner	**Art Unit**
Anne Marie Wehbé	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 7, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-17* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's response received on 2/7/03 has been entered. Claim 18 has been canceled. Claims 1-17 are currently pending in the instant application. An action on the merits follows. Please note that the examiner of record for this application has changed, see page .

The text of those sections of Title 35, US code, not included in this office action can be found in the previous action, paper no. 6.

Applicant's amendments to the specification, specifically the amendments to the title, the abstract, and claim 3, have overcome the objections of record presented on page 3 of the previous office action.

Claim Rejections - 35 USC § 112

The rejections of claims 1-18 under 35 U.S.C. 112, second paragraph, for the omission of essential steps and for indefiniteness are maintained in part. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The previous office action stated that claim 1, and thus claims 2-17 as well, appeared to be missing two essential method steps. In step a) the previous examiner indicated that a

polypeptide isolation step necessary in order to bind the polypeptide to the solid phase is missing. In step b) the previous examiner indicated that an antibody purification step is missing. In regards to the polypeptide isolation step, the applicant argues that a purification step is not needed to bind the polypeptide to the solid phase, and that in fact it is an advantage to the instant method that polypeptide purification is not needed to detect or enrich for the antibody. Step a), as written, recites that the polypeptide expressed by the host cell which is derived from a mammal is bound to a solid phase with the aid of the detection signal. It is not clear from step a) whether the host cell is *in vitro* or *in vivo*. Furthermore, the claims read on polypeptides which may or may not be secreted. In order for a polypeptide expressed from transfected cell *in vivo* to bind to a solid support, it must be removed from the host. In addition, if the protein is not a secreted protein, such as an intracellular protein, then regardless of whether the cells are *in vivo* or *in vitro*, the polypeptide must be released from the cells in order to bind to the solid support. Thus for any of the aforementioned scenarios, isolation of the polypeptide is required in order to bind to the solid support. If the applicant intends the claims to read polypeptides secreted from the host cell, then an isolation step might not be essential in order for the polypeptide to bind to the support. If the applicant intends to claim a method useful for secreted proteins, then amendment of the claims to indicate that the DNA encoding a polypeptide which is linked to a sequence which encodes a detection signal is also linked to a secretion signal sequence is suggested.

In regards to step b), the applicant argues that the purification of the antibody occurs by the reaction of the antibodies formed in step b) with the polypeptide formed in step a). While the

office concurs that step c) effectively provides for a "purification" step in the sense that the antibody when bound to the polypeptide can be further isolated by removal of material that has not bound to the polypeptide/solid support, the step which is lacking in the claim is the step whereby the antibodies are removed from the animal. Step b) only indicates that the antibodies are formed in the animal. The step as written does not indicate that the antibodies are removed from the immunized animal.

In regards to the rejection of claim 1, and thus claims 2-17, for indefiniteness regarding the meaning of , "for the purpose of preparing the desired antibodies, is also used in vitro for producing the target protein", the applicant argues that the recitation of a purpose is not required in the claim and has been removed by amendment. However, the instant grounds for rejection has to do with whether the phrase " is also used *in vitro* for producing the target protein" refers to a separate method step that occurs concurrently with step b), and whether that step is in fact step a). Please note that step a) as written does not include the limitation "*in vitro*". Thus the claim is confusing not because is recited a purpose, by rather because, as stated on page 4 of the previous office action, it is unclear whether step b) includes an *in vitro* step separate from step a). Therefore, applicant's amendment does not overcome this rejection.

In regards to the remaining issues regarding claim 1 discussed on page 4 of the previous office action, the amendments to claim 1 have overcome these grounds for rejection.

In regards to the rejections of claims 7, 8, 10, and 18, applicant's amendments and/or cancellation of the claim has overcome the instant grounds of rejection.

Claims 1-17 are newly rejected under 35 U.S.C. 112, second paragraph, for as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites , "wherein the expression vector employed for the genetic immunization in step (b), ..". Step b) does not recite an expression vector for genetic immunization, but rather a DNA encoding the polypeptide. Thus, there is not antecedent basis for "the expression vector". Furthermore, based on the fact that claim1 appears to indicate that the DNA encoding the polypeptide is present in an expression vector, claim 7 appears to be redundant and fails to further limit parent claim 1.

Claim Rejections - 35 USC § 102

The rejection of claim 18 under 35 U.S.C. 102(b) over U.S. Patent No. 5,639,656 is withdrawn in view of applicant's cancellation of the claim.

Claim Rejections - 35 USC § 103

The rejection of claims 1-3, 5-7, 9-11, and 14-15 under 35 U.S.C. 103(a) over Content et al. in view of Letesson et al. and Ausubel et al., and the rejections of claims 4, 8, 12, 13, 16 over Content et al. in view of Letesson et al. and Ausubel et al. and further in view of Wands et al., or

Barry et al., or Kilgannon et al. or Harlow et al. and Neckelmann et al., are withdrawn in view of new grounds of rejection of the claims under 35 U.S.C. 103(a), see below.

The rejection of claims 1, 2, 5-7, 9-11, 13-15, and 17 under 35 U.S.C. 103(a) over Content et al. in view of Whitehorn et al. is withdrawn in view of new grounds of rejection of the claims under 35 U.S.C. 103(a), see below.

Claims 1-17 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,773,293 (6/30/98), hereafter referred to as Kilgannon et al., in view of U.S. Patent No. 5,736,524 (4/7/98), hereafter referred to as Content et al., and further in view of Letesson et al. (1997) Clin. Diag. Lab. Immunol., Vol. 4, 556-564 and Whitehorn et al. (1995) Bio/Technology, Vol. 13, 1215-1219. The applicant claims processes for producing antibodies which react specifically with a polypeptide comprising immunizing an animal with a DNA encoding the polypeptide linked to a detection signal such that antibodies are formed and reacting the antibodies with recombinant polypeptide bound to a solid support, wherein the recombinant polypeptide is derived from cells transfected with the same DNA encoding the polypeptide. The applicant further claims said processes wherein the signal is an hexa-histidine tag sequence, wherein the DNA sequence encoding the polypeptide is operatively linked to the CMV promoter, or wherein a cytokine expression vector is co-administered to the animal along with the DNA encoding the polypeptide. In addition, the applicant claims said processes wherein the polypeptide

is bound to a microtiter plate or magnetic beads, and wherein the antibody bound to the polypeptide is detected by an anti-antibody and is subsequently released by elution.

Kilgannon et al. ICAM-4/GST fusion proteins wherein the GST can be used as a detection signal for detecting the ICAM-4 fusion protein (Kilgannon et al., columns 7-16). In particular, Kilgannon et al. teaches the use of ICAM-4/GST protein for immunization of mice to make antibodies and hybridomas, and further for detecting anti-ICAM antibodies by coating microtiter plates with ICAM/GST derived from recombinant bacteria and exposing the coated plates to antibodies derived from the hybridomas generated from the immunized mice (Kilgannon et al., columns 15-16). For detecting antibody binding to bound polypeptide, Kilgannon et al. teaches detecting with the bound antibody with goat anti mouse IgG labeled with horseradish peroxidase (Kilgannon et al., column 16).

While Kilgannon et al. teaches that the detection signal in the fusion protein is GST, the use of epitope tags such as hexa-histidine or GPI residues was well known at the time of filing as evidenced by the teachings of Letesson et al. and Whitehorn et al.. Letesson et al. teaches recombinant fusion proteins containing a hexa-histidine peptide at the C-terminus useful for detecting/purifying the fusion protein and for coating microtiter plates in order to detect antibody binding to the fusion protein (Letesson et al., pages 557-558). Whitehorn et al. teaches recombinant fusion protein containing a GPI anchor at the C-terminus useful for detecting/purifying the fusion protein following cleavage of the GPi anchor (Whitehorn, page 1215). Whitehorn et al. also teaches that the GPI residue tag sequence can be used to bind the

polypeptide to a solid surface using antibodies which recognize the tag sequence, and that the polypeptide can be further used to detect antibody binding to the polypeptide of interest. Thus, based on the motivation to use various epitope tags to detect fusion protein expression and the use of fusion proteins containing GST, hexahistidine tags, or GPI residues, in immunoassays for detecting antibody binding, it would have been *prima facie* obvious to the skilled artisan to substitute other well-known detection signals such as hexahistidine for GST in the methods of making and using ICAM-4 fusion proteins taught by Kilgannon et al. Further, based on the high level of skill in molecular biology, the skilled artisan would have had a reasonable expectation of success in modifying the vector taught by Kilgannon et al. to include a hexahistidine epitope tag or a GPI tag.

While Kilgannon et al. teaches the production of the polypeptide fusion protein by transfecting cells with a recombinant DNA encoding the polypeptide, Kilgannon et al. does not teach the direct injection of DNA encoding the polypeptide into mice in order to generate antibodies. Content et al. supplements Kilgannon et al. by teaching the generation of antibodies *in vivo* in mice by direct administration of a DNA plasmid vector encoding a polypeptide of interest (Content et al., columns 10-13 and 17). The DNA plasmid vector can be administered by direct intramuscular injection or by a jet injector using gold microprojectiles coated with the DNA (Content et al. column 2). Please note that the jet injector is commonly referred to as a "gene gun". Content et al. further teaches that vectors encoding a polypeptide operatively linked to the CMV promoter and BGH transcriptional termination sequence (polyA sequence) can be used not

only to express the polypeptide *in vivo*, but also to produce the protein in cells *in vitro* (Content et al., columns 10-14). In particular, Content et al. teaches that polypeptide produced by transfecting mammalian cells *in vitro* can be bound to a solid support and used in immunoassays to bind antibody specific for the polypeptide (Content et al., columns 14 and 16-17). In addition, Content et al. teaches the enhancement of immunization by the co-administration of DNA encoding the polypeptide and DNA encoding immunostimulatory cytokines (Content et al., column 9). Finally, Content et al. provides motivation to use eukaryotic vectors instead of protein to generate antigen specific antibodies *in vivo.* Content teaches that its better to immunize with a gene rather than a gene product for the following reasons: 1) the simplicity with which native or nearly native antigen can be presented to the immune system using genetic immunization, and 2) the fact that mammalian proteins expressed recombinantly in bacteria for use as antigens in mammals often require extensive treatment to insure appropriate antigenicity (column 9, lines 60-66). In view of the motivation provided by Content et al. to use a gene rather than a gene product to produce antibodies *in vivo*, it would have been *prima facie* obvious to use a DNA encoding the ICAM-4/GST fusion protein in the methods of Kilgannon et al. rather than a polypeptide made in bacteria. Further, based on the high level of skill in the art of molecular biology and the specific teachings in Content as to mammalian expression vectors useful for both producing antibodies *in vivo* and producing protein in mammalian cells *in vitro*, the skilled artisan would have had a reasonable expectation of success in modifying the expression vectors taught by Content et al. to include the polypeptide fusion protein taught by Kilgannon et al., and in using the modified vector

to generate antibodies *in vivo* and in producing protein in mammalian cells *in vitro* useful for detecting the antibody by immunoassay.

Please note that applicant's arguments regarding the teachings of Content et al. and Letesson et al. are moot in regards to the instant rejection, since the instant rejection relies on Kilgannon et al. as the primary reference for teaching fusion proteins comprising polypeptides and detection signals. Letesson et al. is cited as evidence that other "detection signals", commonly referred to as epitope tags, were well known in the prior art. Content et al. is cited for providing motivation for using genetic immunization over protein immunization. Although Kilgannon was cited as a secondary reference in the previous office action, the applicants have not addressed the teachings of Kilgannon et al. Furthermore, in regards to applicant's "unexpected result" of increased antigenicity of the expressed polypeptide, it is noted that the claims as written do not include any language regarding the efficacy of antibody production.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Fri from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be

directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER